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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,797	BRAZZELL ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8,27-33,38-41,43 and 45-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,27-33,38-41,43 and 45-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 11/30/04. The amendment filed 11/30/04 is acknowledged. The amendment has been entered. Claims 1-38, 27-33, 38-41, 43, 45-50 are currently pending in the application and are addressed herein.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-3, 7, 8, 27, 28, 30, 31 and 43-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Leboulch et al. (WO 99/26480, cited as IDS reference AN), for the reasons of record, reiterated below.

As indicated in the previous Office Action, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering a to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis

in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33). Therefore, Leboulch anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of Keshet et al. (Journal of Clinical

Investigation, 1999) and further in view of Otani et al. (Investigative Ophthalmology & Visual Science, 1999).

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering a to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that the method can be used to treat choroidal neovascularization.

Keshet et al. teaches that endostatin is an antiangiogenic peptide that inhibits VEGF activity. Specifically, Keshet et al. teaches, " Endostatin was shown to inhibit VEGF-induced endothelial cell migration in vitro and to have anti-tumor activity in vivo, without any apparent signs of toxicity." (See p. 1500, 1st column, lines 3-6).

Furthermore, it was recognized in the art that vascular endothelial growth factor (VEGF) is involved in choroidal neovascularization (CN). For instance, Otani et al. teaches,

> "Recent histological and immunohistochemical studies of experimentally produced and surgically excised CNVMs [choroidal neovascular membranes] have indicated that VEGF, transforming growth factor beta (TGFβ), acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) are involved in the mechanism of CNVM

> formation associated with ARMD [age-related macular degeneration]. Because VEGF has great selectively for endothelial cells, it is considered to be a critical angiogenic factor in the development of CVMN, even though the mechanism of CNVM is not fully understood." (Emphasis added; see paragraph bridging pages 1912-1913).

It is also noted that Otani et al. teaches, "Present findings that Ang2 and VEGF are co-upregulated and that Tie2 is expressed in a variety of cell types in CVNMs further support a crucial role of the interaction between VEGF and Ang2 in pathologic angiogenesis of CNVM formation." (See p. 1912, Abstract).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by Leboulch to ameliorate or reduce the rate of choroidal neovascularization in a subject with a reasonable expectation of success.

The teachings of the prior art indicate that Endostatin is an antiangiogenic factor that inhibits VEGF activity, and Endostatin can be used in gene therapy methods to inhibit neovascularization. The motivation to use the method of Leboulch to inhibit choroidal neovascularization is provided by the teaching in the prior art that VEGF is involved in the development of choroidal neovascularization (See Otani as indicated above).

Claims 1 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,106,826 (Brandt et al.).

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering a to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that

the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is administered intravitreally.

Brandt teaches gene therapy vectors which can be used to deliver therapeutic genes for gene therapy, and specifically teaches an HSV vector as well as an adenoviral vector and adeno-associated vector for use in gene therapy of the eye wherein the vector can be delivered to the eye by intravitreally injecting the vector as well as subretinally and intraocullarly delivering the vector, for therapeutic purposes, such as macular degeneration. (e.g., see abstract, column 5, lines 5-20, column 8,lines 57-65, and column 9 lines 15-20).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method taught by Leboulch such that the vector used was delivered intravitreally with a reasonable expectation of success.

The motivation to modify the method of Leboulch is supplied in part by Brandt who specifically teaches that intravitreal delivery of a therapeutic vector is an effective way to administration for gene therapy for eye diseases.

Claims 1, 33 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.).

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering a to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is a lentiviral vector or that that the vector is a bovine immunodeficiency viral vector.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the gene therapy vector used is the bovine immunodeficiency viral vector taught by Poeschla (which is a lentiviral vector) with a reasonable expectation of success.

The motivation to make such a modification is provided by Poeschla. Poeschla teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

Claims 1, 33, 38-41 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.) and further in view of US Patent 6,106,826 (Brandt et al.).

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering a to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is a lentiviral vector such as a bovine immunodeficiency viral (BIV) vector or that the lentiviral/BIV vector is administered intraocularly, subretinally or intravitreally.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Brandt teaches gene therapy vectors which can be used to deliver therapeutic genes for gene therapy, and specifically teaches an HSV vector as well as an adenoviral vector and adeno-associated vector for use in gene therapy of the eye wherein the vector can be delivered to the eye by intravitreally injecting the vector which would necessarily encompass sub-retinal as well as intraocular delivery (e.g., see abstract, column 5, lines 5-20, column 8, lines 57-65, and column 9 lines 15-20).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the bovine immunodeficiency viral vector taught by Poeschla (which is a lentiviral vector) is used to deliver and express the therapeutic gene and to deliver the lentiviral/BIV vector by intravitreally, subretinally or intraocullarly injecting the gene therapy vector with a reasonable expectation of success.

The motivation to make such a modification is provided in part by Brandt who specifically teaches that adenoviral and AAV vectors can be used to treat eye disease by intravitreally, subretinally or intraocullarly delivering the therapeutic vector; and in part by Poeschla who teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

Response to Arguments

Applicant's arguments filed 11/30/04 have been fully and are addressed below.

With respect to the rejection of claims under 35 USC 112, second paragraph and 35 USC 112, first paragraph, the amendments to the claims overcome the rejections and the rejections are withdrawn.

With respect to the rejection of claims under 35 USC 102(b) based on the teaching of Leboulch, Applicants argue that there is precedent that stands for the proposition that a mere "shotgun" recitation of a number of species of a genus, does not always anticipate every species contained therein (See p. 7-10 of the response). Applicants argue that WO 99/26480 teaches at pages 11-14 possibly all conceivable means for administering a biological drug, and assert that an artisan would have a large list of delivery means from which to choose and to test to obtain the instantly claimed invention, and it is well known that different delivery means can have an impact on bioavailability. Applicants contend that there is no highlighting and teaching of direct administration to the eye as claimed in the Instant application. Furthermore, Applicants argue that the working examples of WO 99/26480 teach only ex vivo transduction and engraftment of the transformed cells by standard subcutaneous, intravenous or intraperitoneal implantation and contend that none of the working examples teaches direct administration of a vector to the eye. The Applicants also contend that the PCT also focused primarily on treating cancer, and assert that angiogenesis is a complicated process wherein numerous different effector cells are involved and varies from tissue to tissue, etc.

In response, it is respectfully pointed out that although the Working Examples of the WO 99/26480 document teach ex vivo methods, page 2 (last full paragraph) of the document clearly

teaches ex vivo and in vivo methods and identifies in vivo therapy as a preferred embodiment. Furthermore, the ex vivo and in vivo methods taught by WO 99/26480 preferably involve delivery of the angiogenesis inhibiting polypeptide using a viral vector or plasmid which can be administered so that cells of the patient in the vicinity of the tumor are infected or transfected with the nucleic acid encoding the angiogenic-inhibiting polypeptide. Furthermore, like the instant application, the WO document teaches in detail a number of different viral vectors that can be used to deliver and express the therapeutic endostatin protein (e.g., see p. 5). The WO document indicates that the term "a gene therapy vector" is meant to mean a vector useful for gene therapy and can be a virus, plasmid or phage (p. 5). Furthermore, the WO document teaches, "preferred vectors include, e.g., retroviral vectors, adenoviral vectors, adeno-associated vectors, herpes virus vectors, Similiki Forest Virus-based vectors, Human Immunodeficiency Virus, Simian Immunodeficiency virus, and non-viral plasmids (p. 5). Additionally, p. 9 of the WO document teaches in detail a preferred embodiment in constructing a gene therapy vector that is sufficient for use in the treatment of angiogenesis in vivo. All of the above coupled with claim 33, which is drawn to making a medicament, but which clearly indicates that the medicament can be used to treat a human patient suffering from diabetic retinopathy wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the retina, and p. 14 clearly indicates that the eye is a specific target for the delivery of the therapeutic nucleic acid.

Therefore, all of the above taken together not only teach every limitation of the claims, but also provides sufficient guidance to reasonably enable a direct application of an endostatin expressing vector to mitigate or reduce angiogenesis. It is noted that the level of predictability

parallels what is taught in the prior art regarding gene therapy of the eye as well as gene therapy for treating a tumor and/or angiogenesis in a patient in need of treatment by direct administration of a gene therapy construct. For instance, US Patent 6,638,502 teaches direct administration of a gene therapy vector expressing an anti-angiogenic factor for treatment of tumors (e.g., see the working Examples). Also, see US Patent 5,827,702, which teaches using a recombinant adenoviral vector for delivery of a gene of interest to different parts of the eye. For instance, the '702 patent teaches directly delivering the vector to choroid ocular cells in a mouse wherein a gene of interest encoded by the vector is expressed in the choroids ocular cells (e.g., see Example 3). Also see the previously cited prior art including US Patent 6,201,104, US Patent 6,106,826, US Patent 6,555,107, which also indicate the state of the prior art of gene therapy of the eye. Additionally, the instant specification also acknowledges numerous techniques for increasing gene expression in the eye by direct administration (e.g., see p. 8, p. 9--especially the third full paragraph, p. 10, p. 11 and p. 13)

Furthermore, regarding applicants assertion about the complexity of angiogenesis, the fact that angiogenesis a complex process which involves a number of different interplaying factors, does not necessarily mean that the WO document's teachings neither anticipates nor enables the claimed invention. In fact, every element and/or limitation of necessary for the practice of the claimed invention is taught in detail in the WO document. Also, as indicated herein, it was recognized in the prior and post filing art that endostatin inhibits VEGF activity and VEGF activity is involved in angiogenesis, including diabetic retinopathy neovascularization and choroidal neovascularization (e.g., see the publications cited above and Seo et al., American Journal of Pathology, 1999 as well as Kwak et al., Investigative Ophthalmology & Visual

Science, 2000.). Taken as a whole the prior art indicates endostatin could be used to treat neovascularization/angiogenesis in the eye regardless if the disorder is retinal neovascularization/angiogenesis or choroidal neovascularization/angiogenesis as VEGF was recognized as involved in both processes.

With respect to Applicants arguments regarding the '104 patent, Applicants arguments are persuasive and the rejections based on the '104 patent are withdrawn. However, it is noted that a new grounds of rejection has been set forth based on the teachings of Leboulch for the reasons indicated herein.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER

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